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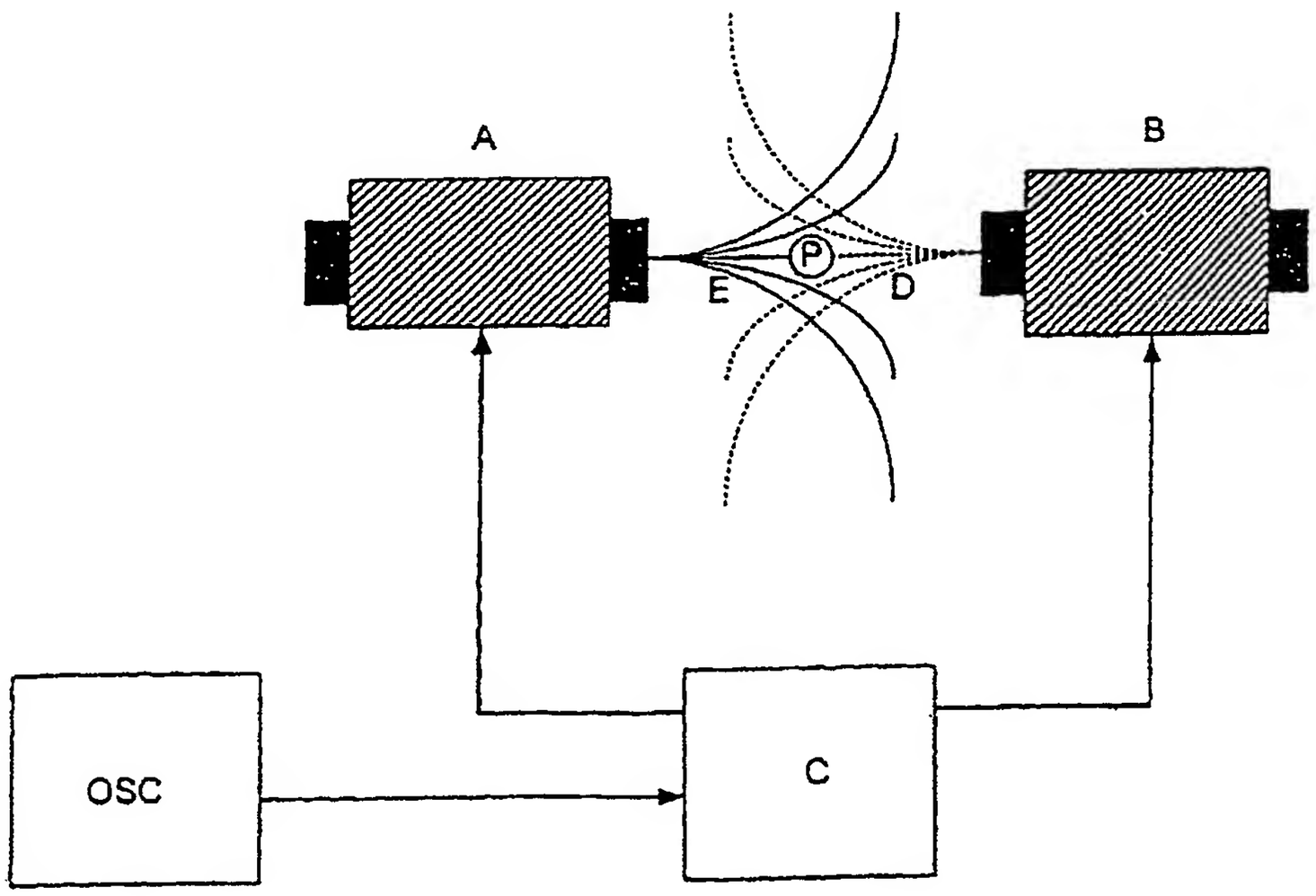
(54) Title: DEVICE FOR THERAPEUTIC PURPOSES ON HUMAN TISSUE, FOR INFLUENCING INJECTED MAGNETIC PARTICLES WITH AN ALTERNATING ELECTRO-MAGNETIC GRADIENT FIELD



(57) Abstract: A new device for therapeutic influence, change, decomposition of various biological structures in vivo or in vitro by means of an externally applied alternating magnetic gradient field is described.

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DEVICE FOR THERAPEUTIC PURPOSES ON HUMAN TISSUE; FOR INFLUENCING INJECTED MAGNETIC PARTICLES WITH AN ALTERNATING ELECTRO-MAGNETIC GRADIENT FIELD.

The present invention relates to equipment for changing, weakening or destroying biological structures in vivo and in vitro by means of a magnetic gradient field.

BACKGROUND OF THE INVENTION

Magnetism and magnetically responsible particles have been used for a long time in various biochemical and medical applications. When paramagnetic materials are exposed to an externally alternating homogeneous magnetic field, heat is generated due to hysteresis. This generation of heat, in particular in combination with superparamagnetic nanoparticles, is used in cancer therapy and is then referred to as magnetic fluid hyperthermia (1). A cancer cell normally has a higher temperature than a healthy cell and therefore does not tolerate as high a temperature rise as a healthy cell. Thus, the cancer cells can be selectively destroyed or weakened without affecting the host organism. An alternative method is that the composition of the superparamagnetic particles is of such type that cancer cells are made to take in said particles into the cell, whereby the temperature is raised more efficiently in the cancer cell without any considerable heat loss to the environment. This type of therapy has been found to be promising, which is described, inter alia, in the patent literature (2, 3, 4, 5), even if there is no clinically approved magnetic equipment for this purpose for the time being.

A cell membrane is, inter alia, composed of lipids and fatty acids, which both have poor thermal conductivity, which makes it difficult to fight the target cell efficiently with only extracellular heat generated by hysteresis.

SUMMARY OF THE INVENTION

According to the present invention, a device is provided which solves the above-mentioned problems. Thus, a device is provided for increasing the thermal and/or kinetic energy of magnetically responsible particles, said device containing at least two magnetic field generating means, of which at least one is a coil, between which means an alternating magnetic gradient field can be generated in a spatially defined area, into which spatially defined area human or animal tissue can be introduced, said alternating magnetic gradient field causing an increase of the thermal and/or kinetic energy of magnetically responsible particles which have been added to said tissue, the increased thermal and/or kinetic energy of the magnetically responsible particles selectively reducing, deactivating or destroying endogenous or exogenous biological structures in said tissue.

In one embodiment of the invention, one of the magnetic field generating means is a permanent magnet.

In another embodiment of the invention, the device contains at least two coils and these coils are fed with alternating currents having different frequencies and/or amplitudes and/or phases, or alternatively said coils are fed with either the positive or the negative part of the fed alternating current.

Furthermore, the device can suitably be equipped with a thermostat for careful temperature control of said tissue and/or with variable time setting for careful control of the time during which said tissue is exposed to the alternating magnetic gradient field.

In one embodiment of the device, the alternating magnetic gradient field alternates with frequencies of up to 30 MHz and the field strength inside said coils amounts to at least 10 mT.

The tissue which is to be treated can be a body part or an inner organ or blood, which are returned to the

host organism after completed exposure to the alternating magnetic gradient field.

The magnetically responsible particles suitably comprise a core of a metal oxide and a coating containing antibodies or parts thereof and have a size of 0.1-300 nm.

The magnetically responsible particles have been added to the host organism before the exposure of its tissue to the alternating magnetic gradient field, or alternatively after the tissue has been temporarily removed from the host organism.

The endogenous or exogenous biological structures consist, for instance, of mammal cells, malignant cells, plant cells, nerve cells, bacteria, viruses, cellular organelles, cell membranes, cell walls, liposomes, proteins, protozoa, parasites, peptides, drugs, toxins, organic compounds, inorganic compounds, or combinations thereof.

According to one aspect, the device is intended for in vivo or in vitro treatment of tumour diseases, endocrine disorders or infectious diseases.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a schematic illustration of the behaviour of magnetically responsible materials in one embodiment of the device according to the invention.

Fig. 2 is a schematic illustration of the structure of one embodiment of the device according to the invention for generating a magnetic gradient field with alternating gradient direction.

Fig. 3 is an illustration of an electronic circuit which can be used to feed the coils in one embodiment of the device according to the invention with alternating current.

DETAILED DESCRIPTION OF THE INVENTION

By the present invention, a new device is provided for use in a completely new method which combines the generation of heat by hysteresis with a powerful intro-

duction of shearing forces. The shearing forces initiate dislocations in the biological structure, for instance in cell membranes, cell walls (in cases where the target cell is e.g. a bacterium) or in intracellular components due to mechanical fatigue, which causes damage in the structures. The method is based on the use of an externally applied gradient magnetic field.

Below, the invention will be described in more detail by means of the drawings, which show embodiments of the invention.

Fig. 1 illustrates how a magnetically responsible particle is affected by a magnetic gradient field. Without the action of an external magnetic field, the dipoles 1 in the magnetically responsible particles are randomly oriented (Fig. 1A). When the particles are exposed to a homogeneous magnetic field 2, the dipoles are oriented according to the direction of the field (Fig. 1B). When the direction of the homogeneous field alternates, the dipoles will alternate according to the field direction of the external homogeneous field. When the applied magnetic field is non-homogeneous, i.e. is a gradient magnetic field 3, the dipoles in the magnetically responsible particles will be aligned with the field direction at the same time as the magnetically responsible particles will move towards the gradient according to Fig. 1C.

Furthermore, by alternating the direction of the gradient, the magnetically responsible particle can be brought into mechanical vibration (due to the influence of forces it will alternately change directions).

Moreover, a combination of said magnetic gradient field with a homogeneous magnetic field can be provided either simultaneously or with a time shift so that a better orientation of the dipoles and greater shearing forces can be obtained.

The generation of a gradient magnetic field whose direction periodically alternates (periodically shifts)

requires a device according to the invention, for instance, as illustrated in Fig. 2. The functional principle is based on two coils A and B (with or without a ferrite core) being placed opposite to each other. A control unit C controls the current through the coils so that only one of the coils at a time has a current flowing through its windings. This alternation of current, whose frequency is controlled by the oscillator (OSC), causes the coils to alternately create the gradient magnetic fields D and E with different gradient directions. A biological structure or a magnetically responsible particle P located between the coils will be exposed to a gradient magnetic field with periodically alternating direction, which will induce a mechanical vibration according to the description above.

The present invention also comprises variants, in which, for instance, the current intensity or its direction through the windings of the coils can be controlled so that more efficient vibrations can be obtained. A very useful special case is to let the gradient direction alternate but maintain the orientation of the dipoles by always letting the field direction be the same. This results in advantages, such as no provision of hysteresis (no generation of heat), while the vibration frequency (=kinetic energy) can be increased since the alternation rate of the dipoles will not be limited by the tendency of the magnetic material to counteract the alternation of the dipole directions.

It is also possible to introduce additional coils to obtain more efficient or more directional vibrations.

Fig. 3 illustrates an example of an electronic circuit which can be used to feed the coils in the device according to the invention with alternating current. The circuit contains an oscillator 4 based on the circuit XR2206, whose output signal 5 is amplified by a power amplifying step 6, which is connected in parallel and based on 5 circuits of the type PBD 3548/1 (manufactured

by Ericsson), whose output signal 7 can drive an alternating current (maximum 1 MHz, 10 A) through one or more coils.

It is obvious to the one skilled in the art that the above-described electronic circuit in Fig. 3 is easy to modify and that the same result can be obtained by means of various alternative prior-art connections of oscillators and power amplifiers.

One example of the connection of the coils is that each coil constitutes a part of an oscillation circuit consisting of a 0.5 Ω resistor, a 127 pF capacitor and a 200 µH coil, which are connected in series, which oscillation circuit is fed with alternating current such as shown in Fig. 3.

An alternating gradient field is obtained between two coils which are part of said oscillation circuit and applied to an electronic circuit each, as shown in Fig. 3, with the difference, however, that the coils are fed with 1.0 MHz and 0.9 MHz, respectively. The variation of the gradient field will be dependent on the difference frequency 1.0 MHz - 0.9 MHz.

It is obvious to the one skilled in the art that the above-described example is easy to modify and that the same result can be achieved by means of various alternative connections and coils.

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CLAIMS

1. A device for increasing the thermal and/or kinetic energy of magnetically responsible particles, characterised in that it contains at least two magnetic field generating means, of which at least one is a coil, between which means an alternating magnetic gradient field can be generated in a spatially defined area, into which spatially defined area human or animal tissue can be introduced, said alternating magnetic gradient field causing an increase of the thermal and/or kinetic energy of magnetically responsible particles which have been added to said tissue, the increased thermal and/or kinetic energy of the magnetically responsible particles selectively reducing, deactivating or destroying endogenous or exogenous biological structures in said tissue.

2. A device as claimed in claim 1, characterised in that one of the magnetic field generating means is a permanent magnet.

3. A device as claimed in claim 1 or 2, characterised in that it contains at least two coils, and that these coils are fed with alternating currents having different frequencies and/or amplitudes and/or phases, or alternatively that said coils are fed with either the positive or the negative part of the fed alternating current.

4. A device as claimed in one or more of claims 1-3, characterised in that it is equipped with a thermostat for careful temperature control of said tissue, and/or that it is equipped with variable time setting for careful control of the time during which said tissue is exposed to the alternating magnetic gradient field.

5. A device as claimed in one or more of claims 1-4, characterised in that the alternating magnetic gradient field alternates with frequencies of up to

30 MHz, and that the field strength inside said coils amounts to at least 10 mT.

6. A device as claimed in one or more of claims 1-5, characterised in that said tissue consists of a body part or an inner organ or blood, which are returned to the host organism after completed exposure to the alternating magnetic gradient field.

7. A device as claimed in one or more of claims 1-6, characterised in that said magnetically responsible particles comprise a core of a metal oxide and a coating containing antibodies or parts thereof and have a size of 0.1 - 300 nm.

8. A device as claimed in one or more of claims 1-7, characterised in that said magnetically responsible particles have been added to the host organism before the exposure of its tissue to the alternating magnetic gradient field, or alternatively that said magnetically responsible particles have been added to the tissue after the tissue has been temporarily removed from the host organism.

9. A device as claimed in one or more of claims 1-8, characterised in that said endogenous or exogenous biological structures consist of mammal cells, malignant cells, plant cells, nerve cells, bacteria, viruses, cellular organelles, cell membranes, cell walls, liposomes, proteins, protozoa, parasites, peptides, drugs, toxins, organic compounds, inorganic compounds, or combinations thereof.

10. A device as claimed in one or more of claims 1-9, characterised in that it is intended for in vivo or in vitro use for treating tumour diseases, endocrine disorders or infectious diseases.

FIG. 1A

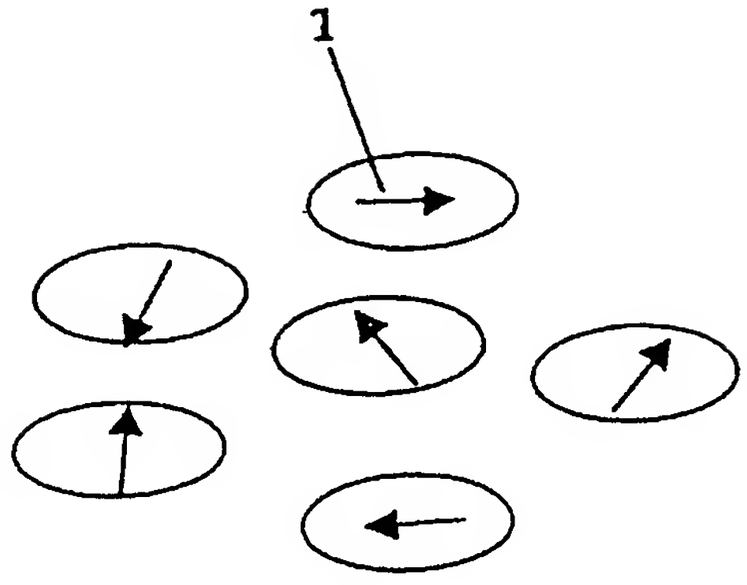


FIG. 1B

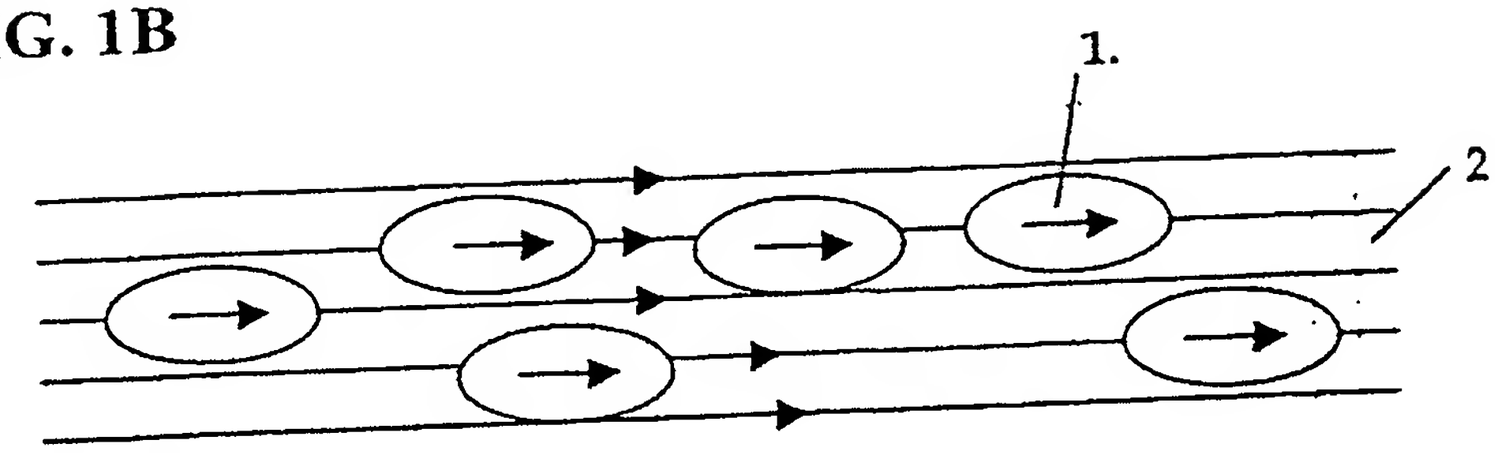
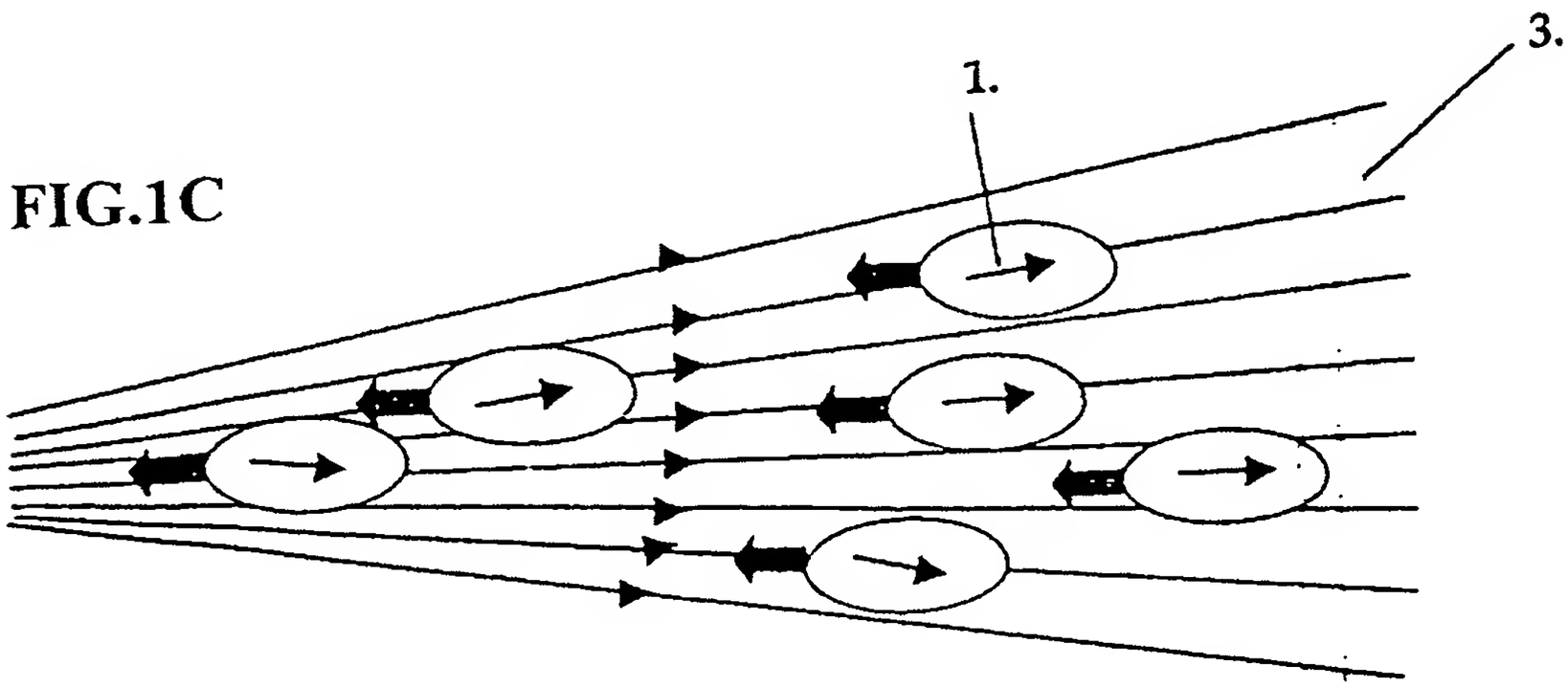
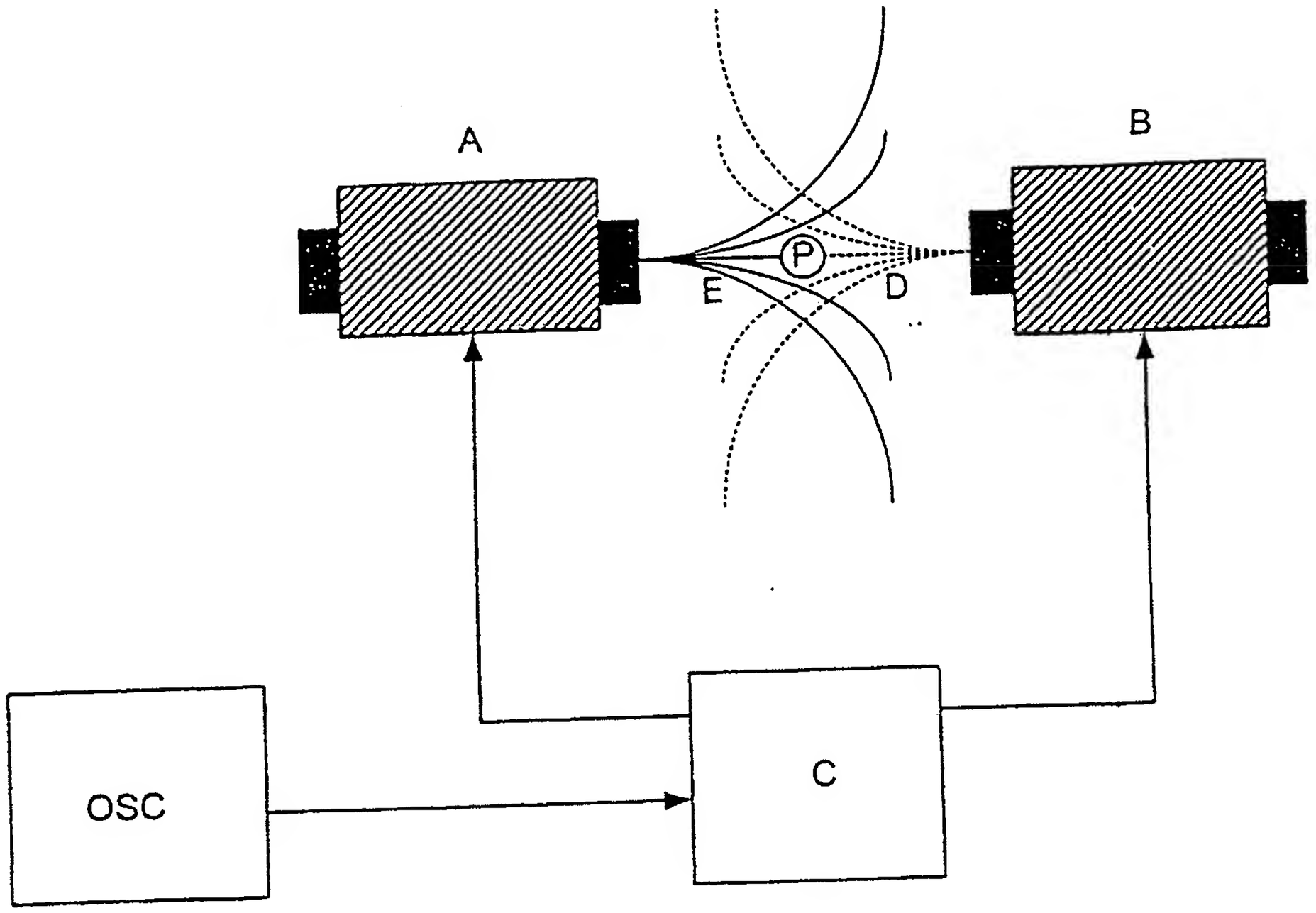


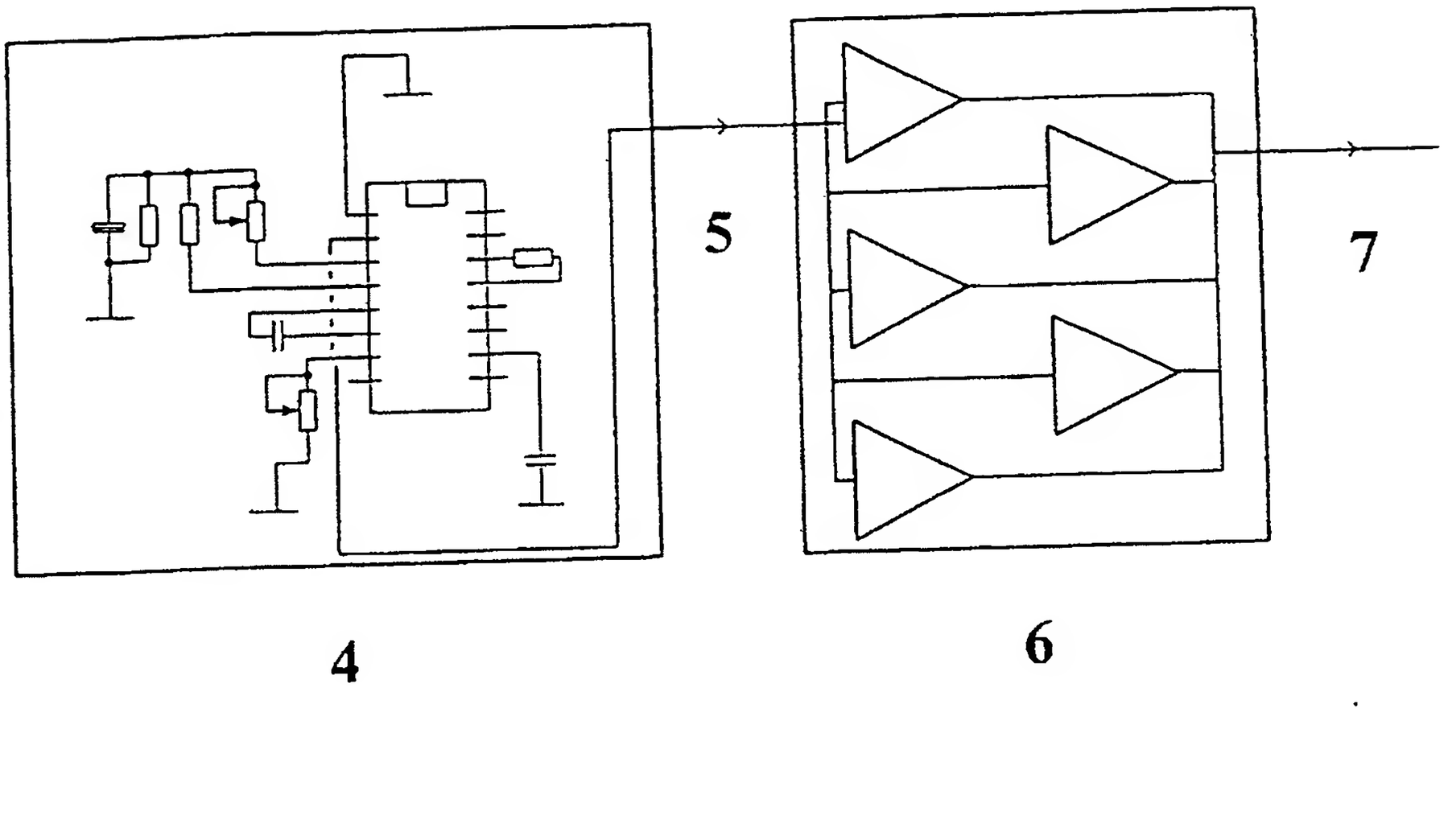
FIG.1C



Figur 1



Figur 2



Figur 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/01730

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61N 2/04, A61N 2/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4983159 A (R.W. RAND), 8 January 1991 (08.01.91), column 3, line 38 - line 52	1-10
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X	US 4303636 A (R.T. GORDON), 1 December 1981 (01.12.81), column 3, line 14 - line 41	1-10
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A	JP 11057031 A 19990302 (DAIICHI KOSHUHA KOGYO KK) 1999-03-02 (abstract) World Patents Index (online). London.U.k.: Derwent Puclications, Ltd. (retrieved on 2000-12-057). Retrieved from: EPO WPI Database. DW199919, Accession No. 99-222966	1-10
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents:

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Date of the actual completion of the international search

7 December 2000

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 00/01730

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4662359 A (R.T. GORDON), 5 May 1987 (05.05.87) ---	1-10
A	RU2080133 C1 (RESHETOV V A) 1997-05-27 (abstract)World Patents Index(online). London, U.K.: Derwent Publications, Ltd. (retrieved on 2000-12-05).Retrieved from: EPO WPI Database, DW199806, Accession No. 1998-061300 --- --------	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

02/11/00

International application No.
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US 4303636 A	01/12/81	US 4106488 A	15/08/78
US 4662359 A	05/05/87	NONE	